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【 CASE REPORT 】

Effective Endoscopic Closure of Cholecysto-duodenal and Transverse Colon Fistulas Due to Squamous Cell Carcinoma of the Gallbladder Using Polyglycolic Acid Sheets and a Covered Metal Stent

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Abstract:

An 81-year-old woman presented with abdominal distension and right hypochondrial pain. Abdominal contrast computed tomography and magnetic resonance imaging revealed an 11-cm gallbladder tumor. The patient was diagnosed with squamous cell carcinoma of the gallbladder by endoscopic ultrasound-guided fine-needle aspiration from the gastric antrum. Thereafter, the gallbladder tumor enlarged, and cholecysto-duodenal and transverse colon fistulas were formed. A covered metal stent was placed on the transverse colon, and polyglycolic acid sheets were injected into the duodenum to close the fistulas endoscopically. Endoscopic closure is less invasive than surgery and considered effective for patients with poor general health conditions.

Key words: gallbladder neoplasms, squamous cell carcinoma, cholecysto-duodenal and transverse colon fistulas, covered metal stent, polyglycolic acid sheet

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Introduction

Squamous cell carcinoma of the gallbladder is a rare malignancy as it accounts for 0.5-2.4% of all gallbladder carcinomas. Its clinical characteristics include large tumor formation, direct invasion into adjacent organs, and probable formation of gastrointestinal tract fistulas (1-3). In cases of fistulas in which radical operation is difficult, surgical closure of these fistulas under general anesthesia is sometimes performed. However, surgery is often contraindicated for elderly patients and individuals with a poor physical condition (4, 5).

The application of polyglycolic acid (PGA) sheets for perforation after endoscopic submucosal dissection (ESD) and gastrointestinal fistula due to malignant tumor has recently been reported (6-9). Furthermore, endoscopic closure with covered metal stent placement can be performed for colovesical or esophagorespiratory fistulas due to colon or esophageal carcinomas (10-12).

To our knowledge, endoscopic closure of gastrointestinal fistulas due to squamous cell carcinoma of the gallbladder has not yet been reported. We herein report a case of effective endoscopic closure with a covered metal stent and PGA sheet for cholecysto-duodenal and transverse colon fistulas due to squamous cell carcinoma of the gallbladder.

Case Report

An 81-year-old woman presented to our hospital com-

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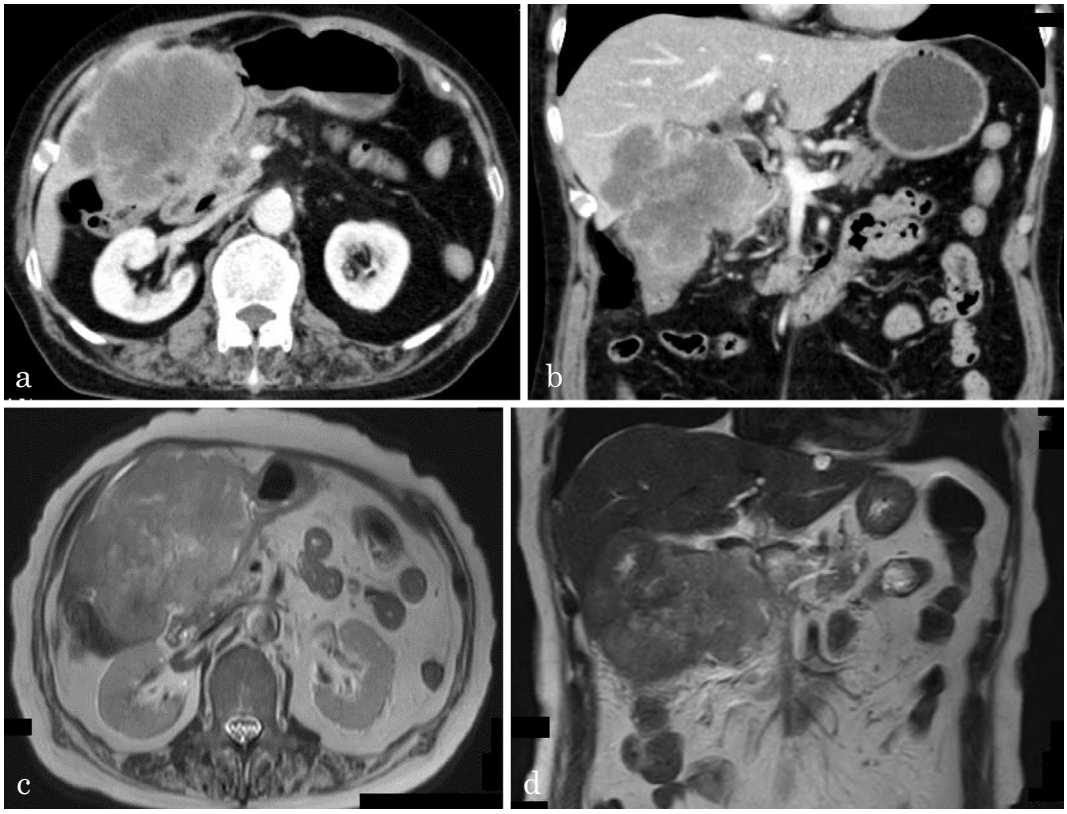

Figure 1. Images of abdominal contrast computed tomography (CT; a, b) and magnetic resonance imaging (MRI; c,d). a-d: CT and MRI revealed a solid tumor of 11 cm in the lower right hepatic lobe and direct invasion into the liver. The tumor was attached to the gallbladder duct and diagnosed as a gallbladder tumor.

plaining of abdominal distension and right hypochondrial pain, and she was admitted for an examination.

Mild tenderness in the right hypochondrium was revealed on a physical examination. Laboratory tests revealed elevated serum inflammatory markers (white blood cells, 13,370/μL; C-reactive protein, 10.4 mg/dL), transaminase, transpeptidase (aspartate transaminase, 36 U/L; alanine aminotransferase, 29 U/L; γ-GTP, 61 U/L), and squamous cell carcinoma antigen (50.3 ng/mL) levels.

Abdominal contrast computed tomography (CT) and magnetic resonance imaging revealed an 11-cm solid tumor in the lower right hepatic lobe attached to the cystic duct (Fig. 1). The gallbladder was not observed despite the lack of a medical history of cholecystectomy. We therefore diagnosed the patient with a gallbladder tumor.

Esophagogastroduodenoscopy (EGD) demonstrated a submucosal tumor-like extrinsic compression along the greater curvature of the gastric antrum (Fig. 2a). Endoscopic ultrasound (EUS) detected an isoechoic mass, and direct invasion into the stomach was considered because the border between the tumor and stomach wall was unclear (Fig. 2b). A histological examination by endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) revealed cell sheets of stratified squamous epithelium, abnormal keratinization, such as single-cell keratinization, and cancer pearl-like structures. Concentrated irregular nuclei of different sizes were observed in keratinized regions (Fig. 2c, d). Therefore, we diagnosed the patient with squamous cell carcinoma of the gallbladder.

She was discharged after EUS-FNA with no complications. Two weeks after discharge, she visited our hospital because a pathological definitive diagnosis was obtained. At that time, she had developed a fever (38.0°C) and reported a poor food intake and difficulty walking. Therefore, she was readmitted to our hospital. CT revealed an enlarged gallbladder tumor, surrounding lymph node metastasis, and substantial gas inside the tumor (Fig. 3a). The border between the tumor and gastroduodenal wall was unclear on CT. Furthermore, the border between the tumor and transverse colon was also unclear. Therefore, the formation of fistulas in the gastrointestinal tract was considered (Fig. 3b). EGD demonstrated a 1.5-cm fistula in the duodenal bulb (Fig. 3c). On a radiological examination using Gastrografin (contrast medium; Bayer Yakuhin, Osaka, Japan), Gastrografin flowed into the gallbladder tumor from the duodenal fistula and then flowed out into the transverse colon from the tumor (Fig. 3d).

Because the tumor was progressing rapidly, chemotherapy was initiated immediately, starting one week after readmission. According to the standard chemotherapy regimen for gallbladder carcinoma, cisplatin and gemcitabine administration was started. However, food intake and stool through the

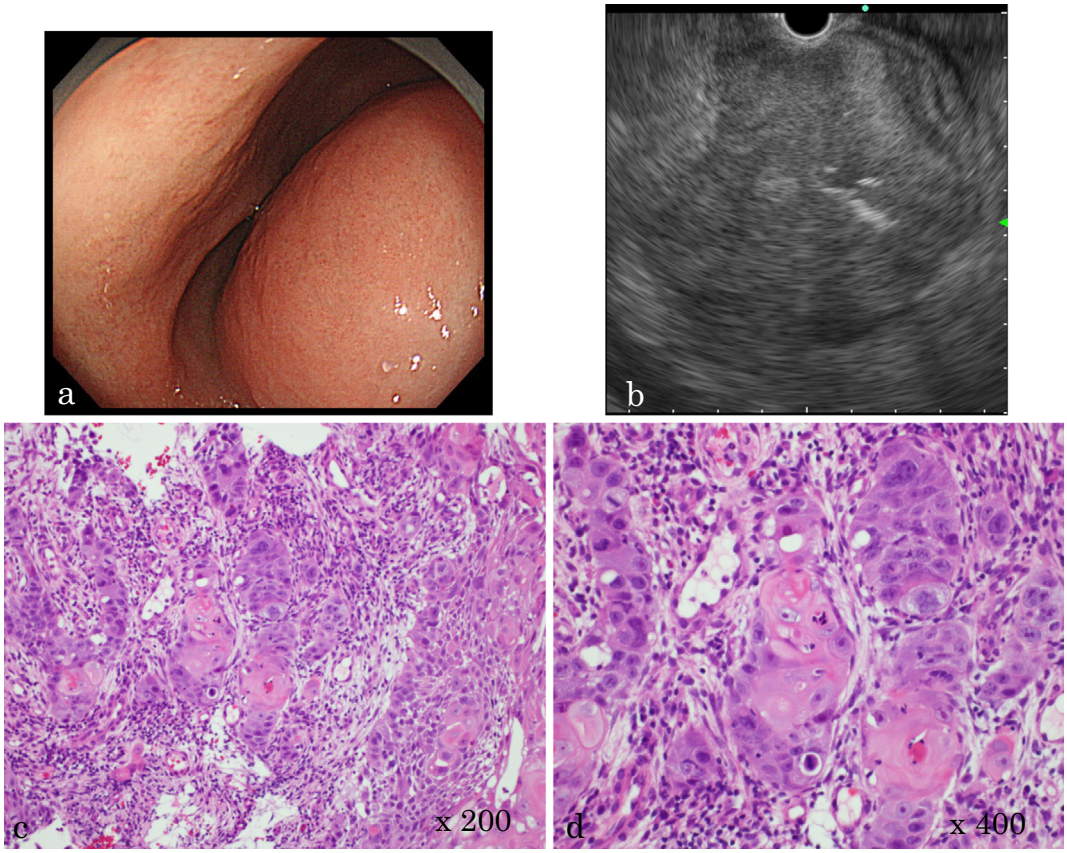

Figure 2. **Findings of esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), and a histological examination by endoscopic ultrasound-fine needle aspiration (EUS-FNA). a: EGD revealed submucosal tumor-like extrinsic compression in the greater curvature of the gastric antrum. b: EUS showed an isoechoic mass, and direct invasion into the stomach was considered because the border between the tumor and the stomach wall was unclear. c, d: A histological examination by EUS-FNA revealed sheets of stratified squamous epithelium, abnormal keratinization, such as single-cell keratinization, and cancer pearl structure. Concentrated irregular nuclei of different sizes were described in the keratinized region. Magnification: c ×200, d ×400.**

cholecysto-duodenal and transverse colon fistulas caused intratumoral infection, and chemotherapy was discontinued. Regarding surgical risks, the American Society of Anesthesiologists physical status (ASA-PS) was low (grade 2), while the age-adjusted Charlson comorbidity index (ACCI) was high (11 points). The patient exhibited undernutrition (total protein, 5.6 g/dL; albumin, 2.0 g/dL); furthermore, both she and her family wished to avoid surgery under general anesthesia because she was 81 years old. Based on these results, the patient was diagnosed with a poor physical status and was not considered suitable for surgery, such as fistula closure or bypass surgery.

As the patient and her family expressed a strong preference for food intake, we decided to attempt endoscopic closure of the fistulas. Closure by clipping or over-the-scope clips (OTSCs) was considered difficult because of the relatively large fistulas in this case. Therefore, we decided to perform closure using a covered metal stent and PGA sheets. Only uncovered metal stents for closure of colon fistulas are considered for insurance coverage in Japan; however, with the consent of the patient and her family, we decided to use a duodenal covered metal stent for the transverse colon fistula. Before treatment, the patient and her family provided their written informed consent.

First, a colonoscopic examination was performed after sedation and pain relief with midazolam and pentazocine. Tract stenosis due to direct invasion of the gallbladder tumor was observed in the transverse colon, along with 2 cm of the fistula (Fig. 4a). For endoscopic closure of the fistula and dilation of stenosis, a covered metal stent (Niti-S covered metal stent 20×12 cm; Taewoong Medical, Seoul, Korea) was placed to seal the fistula (Fig. 4b). Second, EGD was performed. Polygolyc acid sheets (10×5 cm, Neoveil sheet; Gunze Medical Japan, Kyoto, Japan) were cut to the appropriate sizes and applied to the duodenal fistula. Two sheets were used in total, and fibrin glue (Beriplast P Combi-Set Tissue adhesion; CSL Behring, Tokyo, Japan) was applied over the top to fix the PGA sheets in position (Fig. 4c). After application of the PGA sheet, a decrease in Gastrografin, which had been flowing into the gallbladder tumor from the duodenal fistula, was apparent on a radiological examination. Endoscopic closure was successfully

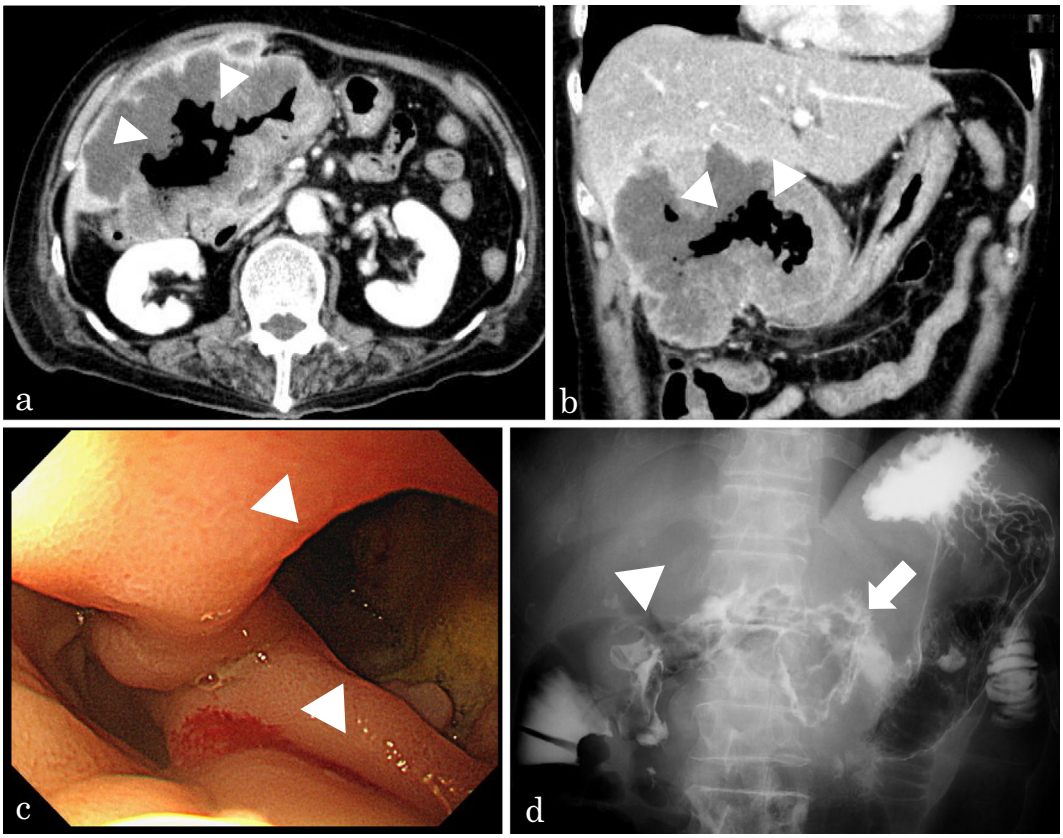

Figure 3. **Findings of computed tomography (CT), esophagogastroduodenoscopy (EGD) and a Gastrografin contrast examination at second admission. a, b: CT revealed an enlarged gallbladder tumor and a large amount of gas inside the tumor (arrowheads). The borders between the tumor and gastric antrum, duodenum, and transverse colon were unclear. Fistulas in the gastrointestinal tract were formed. c: EGD revealed a 1.5-cm fistula in the duodenal bulb (arrowheads). d: Gastrografin flowed into the gallbladder tumor from the duodenal fistula (arrow) and flowed out into the transverse colon from the transverse colon fistula (arrowhead).**

completed without complications.

After performing endoscopic closure of fistulas, fecal vomiting was not observed, and the normal movement of food was achieved. An abdominal radiograph obtained two weeks later did not show stent migration (Fig. 4d). We regularly acquired abdominal radiographs to monitor the position of the stent. Consequently, the patient was able to ingest food orally with no fever. Furthermore, the intratumoral infection was cured, and chemotherapy was resumed. Although the patient died three months after hospitalization due to tumor growth, food intake was possible until one week before her death.

Discussion

Squamous cell carcinoma of the gallbladder forms large tumor lesions, directly invades adjacent organs, and forms gastrointestinal tract fistulas. However, its distant metastasis is rare (1-3). Its prognosis is poor because many cases are discovered at an advanced stage, and the resection rate is lower than that of adenocarcinoma (2). Our case demonstrated all of these characteristics and presented typical clinical features of squamous cell carcinoma of the gallbladder.

Many previous cases of squamous cell carcinoma of the gallbladder have been diagnosed by a histopathologic examination of postoperative surgical specimens. Recently, the usefulness of EUS has been reported, but there have been few reports of squamous cell carcinoma of the gallbladder being diagnosed by EUS-FNA (13-15), which was the method used to establish this diagnosis in our case.

Extended surgery is recommended in cases of squamous cell carcinoma of the gallbladder that form fistulas when there are no issues regarding surgical tolerance. Cases of squamous cell carcinoma of the gallbladder that have been cured by radical surgery were reported to achieve either the same prognosis as adenocarcinoma cases or a significantly better prognosis (16, 17). Therefore, aggressive resection with extended surgery should be performed; however, the resection rate is low due to rapid tumor progression. In cases of fistulas that make radical surgery difficult, surgical closure of fistulas or colostomy under general anesthesia is sometimes performed (4, 5). The ASA-PS and ACCI are often used to predict prognostic performance in patients undergoing surgery (18-20). If the ASA-PS or ACCI is high, the patient is considered to have a poor PS (21). In our case, although the ASA-PS was low (grade 2) because of the lack

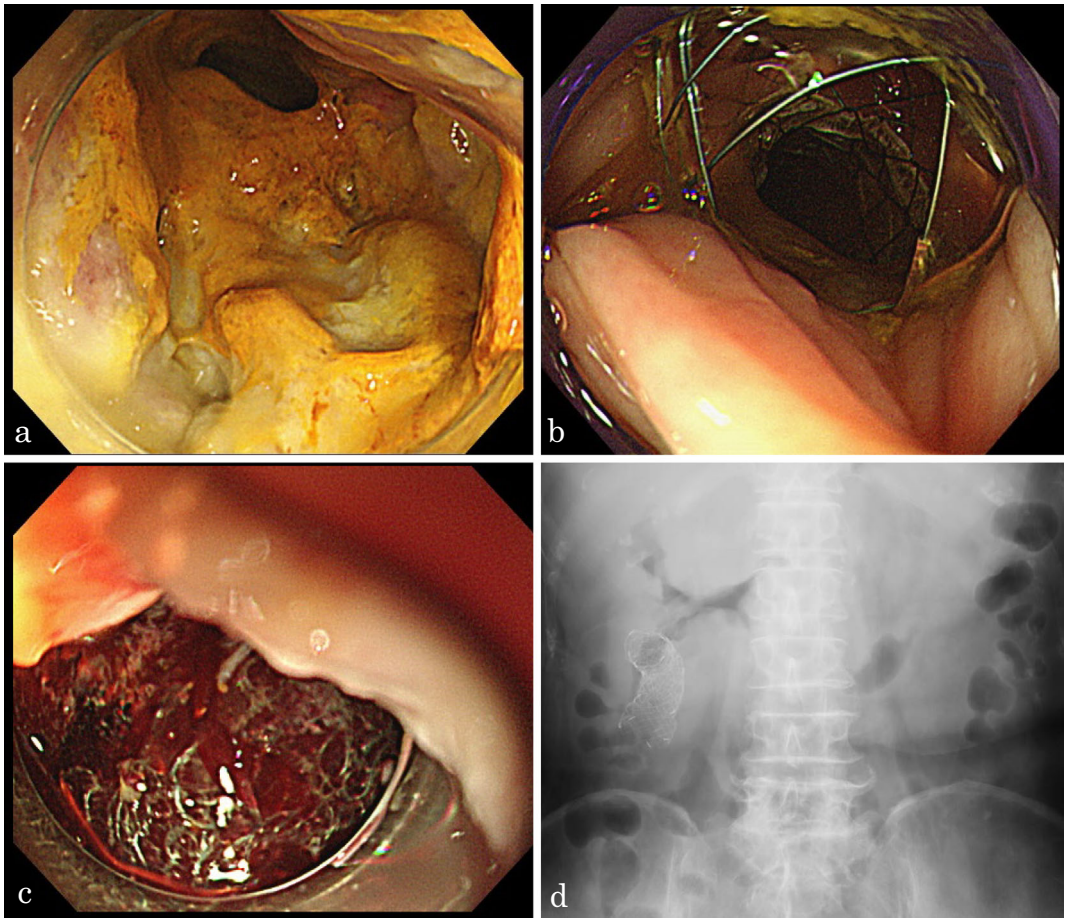

Figure 4. **Findings of colonoscopy, esophagogastroduodenoscopy (EGD), and abdominal radiography. a: Colonoscopy demonstrated stenosis of the normal tract due to direct invasion of the gallbladder tumor and a 2-cm fistula in the transverse colon. b: A covered metal stent was placed so that the cover material sealed the fistula for fistula closure and removal of stenosis. c: Polyglycolic acid sheets, cut to the appropriate sizes, were applied to the fistula of the duodenum, and then fibrin glue was applied. d: An abdominal radiograph obtained two weeks later shows the absence of stent migration.**

of severe systemic complications aside from mild hypertension, the Charlson comorbidity index was high (11 points) because of her advanced age and the presence of a metastatic solid tumor. In addition, because of undernutrition and her advanced age, the patient wished to avoid surgery, which was considered risky and unsuitable. However, a fever due to the backflow of stool persisted. In addition, the patient and her family were strongly in favor of improving her food intake. We therefore performed endoscopic closure of the fistulas.

Endoscopic closure methods for fistulas, such as clipping and OTSCs, are often used (22, 23). Although clipping and OTSCs are effective for small fistulas, these methods are difficult to apply to relatively large fistulas. Recently, PGA sheets, which are often used in the closure of fistulas in respiratory and dental oral areas, have been applied for the treatment or prevention of perforation after ESD (6, 7). Because PGA sheets can be cut to the appropriate size for application, they are considered useful for relatively large fistulas where clipping or OTSCs is not suitable. Therefore, we used PGA sheets to close the duodenal fistula in the present case.

Stent placement therapy for the digestive tract is used to remove stenosis due to malignancy. Covered metal stents have been used for the management of postoperative leakage and fistulas of the upper gastrointestinal tract, such as the esophagus and stomach. The usefulness of covered metal stents is also reported for postoperative leakage and fistulas of the colon (24-27). Furthermore, endoscopic closure with a covered metal stent is also used for fistulas due to malignant tumors, such as esophageal or colon carcinomas that form esophagorespiratory or colovesical fistulas (10-12). Because stenosis in the transverse colon tract was caused by tumor invasion in our case, we determined the risk of stent dislocation to be low and closed the colon fistula by placing a covered metal stent. The use of colonic covered metal stents is currently approved in Japan; however, at the time of the patient's treatment, only uncovered metal stents were covered by insurance. Therefore, we used a duodenal covered metal stent for the transverse colon fistula after obtaining the consent of the patient and family beforehand. Covered metal stents show a higher risk of migration than do

uncovered metal stents. Furthermore, the metal stent may migrate when the tumor size is reduced by chemotherapy. However, the covered metal stent used for the present case has an uncovered portion measuring 15 mm at both ends to prevent migration. In our case, the large tumor compressed the colon where the covered metal stent was placed, and stent migration was prevented. If migration is discovered in the early stage, endoscopic repositioning may be possible. Therefore, it is necessary to confirm the stent position by regular monitoring on abdominal radiographs.

Covered metal stents for colon fistulas, such as those observed in this case, are effective and might be needed in the future. However, in the present case, covered metal stent placement for duodenal fistulas was difficult because the normal tract of the duodenum was not stenotic and was proximal to the pylorus. Therefore, we used PGA sheets to achieve closure of the duodenal fistula. Although complete closure with PGA sheets alone seemed difficult, intratumoral infection was resolved, and resumption of chemotherapy was possible because the backflow of fecal matter into the fistula decreased after placement of the covered metal stent.

In our case, the fever due to the backflow of stool was alleviated, and food intake became possible following endoscopic closure of the fistulas. In addition, chemotherapy was administered to reduce the fistula and tumor masses. However, chemotherapy could not suppress tumor growth, and the patient died three months after hospitalization. If reduction of the tumor had been achieved by chemotherapy, spontaneous closure of the fistulas and life prolongation may have been possible. A regimen of gemcitabine plus cisplatin has been recommended at evidence level A for unresectable gallbladder carcinoma, but the tissue type is not mentioned (28, 29). There are several case reports on chemotherapy using 5-fluorouracil or FOLFOX (folinic acid, fluorouracil and oxaliplatin) as postoperative adjuvant chemotherapy for squamous cell carcinoma of the gallbladder, but no consensus has been reached so far because of the limited number of reports (30). Although gemcitabine and cisplatin, which are considered the standard chemotherapy regimen for unresectable gallbladder carcinoma, were selected in our case, the tumor was not reduced. Chemotherapy regimens for squamous cell carcinoma of the gallbladder should be investigated in future studies.

We performed endoscopic closure with a covered metal stent and PGA sheet for gastrointestinal fistulas due to squamous cell carcinoma of the gallbladder, which enabled food intake. To our knowledge, there are no previous reports of endoscopic closure of gastrointestinal fistulas due to squamous cell carcinoma of the gallbladder. Covered metal stents and PGA sheets are less invasive than surgery and are considered effective for managing relatively large fistulas in which clipping or OTSCs are not applicable.

Informed consent was obtained from the patient and her family for inclusion in the study.

The authors state that they have no Conflict of Interest (COI).

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